SUMMARY MINUTES OF THE

CLINICAL CHEMISTRY AND

CLINICAL TOXICOLOGY DEVICES PANEL MEETING

OPEN SESSION

March 24, 2000

9200 Corporate Blvd.
Room 20 B
Rockville, Maryland

Clinical Chemistry and Clinical Toxicology Devices Panel Meeting

March 24, 2000

PANEL

Acting Chairperson
Martin H. Kroll, M.D.

Voting Members
Barbara R. Manno, Ph.D.
Nader Rifai, Ph.D.
Arlan L. Rosenbloom, M.D.

Temporary Voting Members
Jeffrey A. Brinker, M.D.
Stephen Clement, M.D.
Philip C. Comp, M.D., Ph.D.
James Everett, M.D., Ph.D.
Cassandra E. Henderson, M.D.
Milton Packer, M.D.

Consumer Representative
Stanley M. Reynolds

Industry Representative
Erika B. Ammirati, R.A.C.

FDA PARTICIPANTS

Veronica Calvin, M.A.
Panel Executive Secretary

Jean M. Cooper, M.S., D.V.M.
Branch Chief
Clinical Chemistry and Clinical Toxicology Branch

Steven I. Gutman, M.D., M.B.A.
Director
Division of Clinical Laboratory Devices

Ruth Chesler, B.S., M.T.
Scientific Reviewer
Clinical Chemistry and Clinical Toxicology Branch

Marina Kondratovich, Ph.D.
Mathematical Statistician
Division of Biostatistics

SPONSOR PRESENTERS FOR BIOSITE DIAGNOSTICS

John F. Bruni, Ph.D.
Director, Clinical and Regulatory Affairs

Alan Maisel, M.D.
Professor of Medicine, UCSD

Robert H. Christenson, Ph.D.
University of Maryland

Kenneth F. Buechler, Ph.D.
Biosite Diagnostics

Gunars E. Valkirs, Ph.D.
Biosite Diagnostics

Jeffrey A. Dahlen, Ph.D.
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Brian Chambers
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OPEN SESSION—MARCH 24, 2000

Acting Panel Chairperson Dr. Martin Kroll began the Open Session at 9:32 a.m. **Panel Executive Secretary Veronica Calvin** introduced the topic of discussion, a premarket approval application (PMA) for a peptide test indicated as an aid in diagnosis of congestive heart failure. She briefly summarized the results of the December 6 and 7, 1999 panel meeting, at which the panel unanimously voted to recommend as approvable with conditions a PMA for the GlucoWatch Biographer from Cygnus, Inc., and provided advice and recommendations on over-the-counter vaginal pH devices.

Ms. Calvin introduced Acting Panel Chair Dr. Kroll, substitute Consumer Representative Stanley Reynolds and Industry Representative Erika Ammirati, and noted other panel representatives on loan from the Hematology and Pathology Devices Panel, the Circulatory Devices Panel, and the Cardiovascular and Renal Drugs Advisory Committee. She asked the rest of the panel to introduce themselves. Ms. Calvin read the conflict of interest statement and noted there were no conflicts to report. Ms. Calvin also read the appointment to temporary voting status for Drs. Brinker, Clement, Comp, Everett, Henderson, and Packer.

PRESENTATION

Philip J. Phillips, Deputy Director for Science and Regulatory Policy, FDA, discussed the "least burdensome" provisions of the FDA Modernization Act (FDAMA) of 1997. He cited the references in the Act and examined them in detail, clarifying that FDAMA did not change the standard for clearance and approval of PMAs or 510ks (demonstration of safety and effectiveness or substantial equivalence). Mr. Phillips described the FDA efforts to implement FDAMA through a series of meetings,

publications, and the Least Burdensome Industry Task Force. These efforts have produced an interim FDA definition of least burdensome as the successful means of addressing a premarket issue that involves the smallest investment possible of time, effort, and money. Mr. Phillips addressed whether FDAMA required a change in FDA culture, stressing that there are multiple approaches to satisfying regulatory requirements, that collaboration and compromise are important, and that the spirit of the law should be understood and followed. He stressed there is not a conflict between least burdensome requirements and scientific integrity because good science includes cost effectiveness and all scientific endeavors are affected by availability of resources. Mr. Phillips listed a number of mechanisms to lessen the regulatory burden, such as making sure all regulatory decisions relate to relevant statutory criteria, factoring in all available public information, and using a variety of alternatives to randomized clinical trials. He concluded that it is necessary to factor least burdensome concepts into all premarket activities and to remain open-minded about methods of implementation.

There was a question from the panel about the application of these provisions to the realm of in vitro diagnostic testing.

OPEN PUBLIC HEARING

There were no requests to address the panel.

SPONSOR PRESENTATION

Dr. John Bruni introduced the PMA for the B-Type or Brain or Brain-derived Natriuretic Peptide (BNP) Test. In his overview, he summarized the history of natriuretic peptides and the physiological and pathophysiological studies that have been performed to establish the significance of BNP in left ventricular dysfunction (LVD) and congestive

heart failure (CHF). Dr. Bruni discussed the potential clinical applications of BNP in the diagnosis of heart failure, as a screening test for LVD, and in ventricular remodeling following acute myocardial infarction. He looked at statistics on heart disease and the progression of cardiovascular disease before describing the device as a point of care assay system with a portable instrument and disposable device. He noted that it provides easier, faster monitoring than current lab-based systems, and he outlined the steps involved.

Dr. Bruni discussed the use of the New York Heart Association (NYHA) classification that can be combined with statistical analyses to show that the concentrations of BNP increase with severity of disease. He outlined potential intended uses as an aid in the diagnosis of congestive heart failure, in the diagnosis and management of patients with CHF, or as a point of care test for the diagnosis and management of patients with CHF.

Dr. Bruni presented statistics on concentrations of BNP in hypertensive versus normal men and women. He looked at sensitivity, specificity, agreement, and positive and negative predictive values at various cut-off levels for a range of ages.

Dr. Alan Maisel discussed BNP in the emergency department and assessment of left ventricular dysfunction. He presented statistics on heart failure and noted the need for but difficulty of correct diagnosis in the emergency room, where dyspnea is unspecific in the elderly and obese and echocardiography is limited and costly. Dr. Maisel described two methods of assessing such patients. The first involved 250 patients presenting to the emergency department with shortness of breath, for whom data were recorded and assessment made while BNP values were recorded. The second was a later, "gold

standard" assessment by two cardiologists with access to any later tests such as echocardiography and other information. He presented a graph showing BNP levels of patients diagnosed with CHF, baseline LVD, and without CHF and then showed a univariate analysis of signs such as wheezing and murmurs and of BNP levels in predicting heart problems. He showed ROC curves for BNP and diagnosis and distribution of misdiagnosed cases using BNP at the 80pg/ml cut-off.

Dr. Maisel stated that while echocardiography is the cornerstone for diagnosis of LVD, it is expensive, not always readily available, and sometimes difficult to perform. He hypothesized that BNP levels might serve as a screening blood test in patients referred for echocardiography for evaluation of LV function. After looking at the patient characteristics in this study, he analyzed mean BNP levels for normal versus abnormal LV function and mean BNP levels for systolic versus diastolic LV dysfunction. BNP statistics in the echocardiography study included sensitivity, specificity, positive predictive and negative predictive values, and accuracy at various cut-off levels. He also looked at patient demographics for normal versus abnormal LV function in the echo study and the distribution of patient referral for echocardiography. Dr. Maisel concluded by asking for guidance from the panel on the best intended use for the device.

Questions for Sponsor

Questions from the panel concerned differences between male and female response to the device, the area where the device fits into the clinical evaluation of patients with congestive heart failure, and the selection of patient and control groups. The panel also commented that the control group was extremely small.

FDA PRESENTATION

Ruth Chesler, FDA reviewer, introduced the FDA review team and gave a brief summary of the basic principles of device operation. She explained that the Triage BNP test is a fluorescence immunoassay with a single-use cartridge that uses whole blood or EDTA plasma. She noted that the sponsor measured BNP levels in three different populations: normal subjects, hypertensive subjects without congestive heart failure, and congestive heart failure subjects. The studies were conducted at four clinical sites, which she described. Patients were selected sequentially, and patients in each of the New York Heart Association classes were studied. She provided data on the patients studied, noting that age was not provided on all patients, although literature notes that BNP levels increase with age. Ms. Chesler explained how the sponsors conducted precision studies and showed the precision results as they are proposed for product labeling. Sponsors tested various substances for possible interference, only two of which showed interference levels of 10% or greater.

Dr. Marina Kondratovich, from the FDA Division of Biostatistics, discussed the age-matched ROC analysis for healthy subjects versus all CHF and healthy subjects versus patients with CHF from classes I and II, as well as hypertensive versus all CHF and hypertensive versus CHF class I and II. She noted that it is important that the diseased group and non-diseased group are age-matched because BNP increases with age. Without such age matching, sensitivity and specificity are overstated. Dr. Kondratovich showed how the ROC age-matched analysis produced different specificities and sensitivities at various cut-offs. Age-matched ROC analysis separately for females showed that the test has almost the same characteristics of performance, but because females have a tendency to have bigger values of BNP, gender also contributes to

potential misclassification of CHF subjects. She stated that precision, which is 12-16%, and drug interference can also contribute to potential misclassification of CHF patients but do not affect significantly the ability of the test to separate CHF patients from other categories.

Before concluding the FDA presentation, Ms. Chesler read the five questions for panel discussion.

Questions for FDA

Panel questions to the FDA presenters focused on whether the small number of observations could give statistical power, the effect of the limited elderly population on ROC curves, whether the CVs were reasonable, commercially available peptide tests, and use of the test with African Americans subjects.

OPEN COMMITTEE DISCUSSION

One panelist noted concerns with the lack of data or information on comparison to commercially available peptide tests, standardization, frequency and type of calibration verification, stability of the calibrators and controls, linearity of method, and interference with renal failure patients. Another panelist's comments focused on the imprecision, logistics of the clinical trial, need for evaluating functional sensitivity, internal calibration, use with women, and validation of the intended use setting. Another panelist raised concerns involving the diabetes subpopulation, followed by one who listed five questions to be answered. They included whether the assay reliably measures the peptide, whether the level of peptide correlates to pathophysiologic conditions, whether the peptide level is affected by other metabolic processes or pharmacologic manipulations, what the likelihood of misinformation is, and what else the sponsor can do

to improve the data set or to better direct device use. A question was raised about whether the only effective population for the test was in young males and if patients on estrogen supplements were included in the normal population.

OPEN PUBLIC HEARING

Gary Robinson of IGEN pointed out that the prevalence of congestive heart failure was not presented in the material, which raised questions for him about the predictive value of the test.

OPEN COMMITTEE DISCUSSION

FDA Questions to the Panel

Ms. Chesler then read the FDA questions to the panel for discussion.

In answering the first of the FDA questions for discussion, the majority of the panel thought that the limitations of an age-matched analysis are already clear in that the sensitivity and specificity in the real intended population are not shown. As age of the patient increases, the cutoff should also increase and a higher cut-off is appropriate, but there are no data to provide the basis for decision.

The panel expressed a reservation that the second question assumed an automatic approval of the device. Dr. Gutman acknowledged an assumption from the review team that the device can meet the least burdensome provisions for approval but stressed that the panel was free to give scientific advice to the contrary. He also clarified that there were two issues involved: performance in point of care versus controlled laboratory settings and performance in pre-selected population bases. The panel had a diversity of response, with some members thinking it important to include in the labeling the fact that studies were done by trained laboratory personnel and not in real-world use.

On possible ways to portray the data and calculate sensitivity and specificity, the panel recommended including all the comparisons listed, with a summary of the data so people can understand the potential variable performance of the assay.

The panel thought evaluation of the cut-off using age-matched data and ROC curves was not relevant to the disease-bearing population and stated that more data that would allow analysis were needed before reaching a conclusion on the cut-off.

The panel recommended that the BNP results stratified by NYHA classification should remain in the labeling, but recommended adding that there is still significant potential for error in the stratification. One member noted it would be interesting to know if this stratification applies to diabetics or if diabetes makes a difference in the stratification.

FINAL RECOMMENDATIONS AND VOTE

Executive Secretary Veronica Calvin read the voting instructions and options.

A motion was made and seconded to recommend the PMA as nonapprovable. In discussion, the motion was opposed by those who saw value to the test not to detect class 1 or 2 heart failure but as an aid in differential diagnosis of heart failure symptoms and in follow-up of heart failure. In addition, they felt the labeling could be cautiously worded. The panel discussed whether approval pending collection of further data was feasible, citing concerns about performance of the test in older men and women with CHF. The motion to recommend the PMA as nonapprovable was passed by a vote of six to three.

Sponsor Comments

Representatives for the sponsors commented that despite its shortcomings, the product has clinical utility as an aid in the diagnosis of CHF and thanked the panel for its review.

Panel Comments

Panel comments focused on technical aspects that had not been substantiated and the need for sponsors to address deficiencies in the data by getting more data on the normal, healthy elderly population and on the elderly with other illnesses such as mild hypertension and renal insufficiency as compared to major heart failure. It was suggested that the sponsors look for a limited indication with more focused data and a careful screening of the control group.

Dr. Kroll thanked the panel, sponsor, representatives, and the FDA review team and adjourned the meeting at 4:00 p.m.

I certify that I attended the meeting of the Clinical Chemistry and Clinical Toxicology Devices Panel on March 24, 2000, and that these minutes accurately reflect what transpired.

Veronica J. Calvin

Veronica Calvin
Executive Secretary

I approve the minutes of this meeting as recorded in this summary.

Martin H. Kroll, MD 8/30/00

Martin H. Kroll, M.D.
Acting Chairperson